NAVAL SUBMARINE MEDICAL RESEARCH LABORATORY

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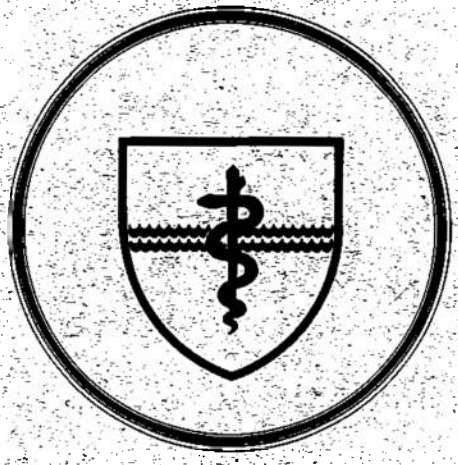

REPORT NUMBER 963

DRUGS EXPOSED TO EXTREME COLD:

The Military Perspective

by

Michael L. Shea, Robert M. DeBell, Kenneth R. Bondi
and
Robert A. Margulies

Naval Medical Research and Development Command
Research Work Unit MF58.524.013-1036

Released by:

William C. Milroy, CAPT, MC, USN
Commanding Officer
Naval Submarine Medical Research Laboratory

11 November 1981

DRUGS EXPOSED TO EXTREME COLD: THE MILITARY PERSPECTIVE

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REPORT NUMBER 963

NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
RESEARCH WORK UNIT F58524 MF58524013-1036

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SUMMARY PAGE

PROBLEM

To identify the changes in the pharmaceutical properties of drugs exposed to extreme cold.

FINDINGS

A list of drugs identified as being damaged by freezing (68 of 153 items) was excerpted from the 668 Authorized Medical Allowance List (AMAL). Freeze/thaw stability data was obtained from both the literature and innovator drug companies for over one half (45 of 68) of these items. A summary of recommendations for use in cold operations of these 68 items was prepared. Recommendations ranged from conservative (in those cases where no information was available) to liberal (where drug companies were concerned about efficacy). Recommendations also included the substitution of some items on the list with drugs of similar action but not needing freeze protection.

APPLICATION

Requirements for proper storage of certain drugs in a cold weather environment will help to maximize the effectiveness of medical support.

ADMINISTRATIVE INFORMATION

This investigation was conducted as part of Naval Medical Research and Development Command work unit - 62758N F 58524 MF58524013-1036. The present report is No. 1 on this work unit. The manuscript was submitted for review on 9 September 1981, approved on 11 November 1981, and designated as Naval Submarine Medical Research Laboratory Report No. 963

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ABSTRACT

A list of drugs identified as being damaged by freezing (68 of 153 items) was excerpted from the 668 Authorized Medical Allowance List (AMAL). Freeze/thaw stability data was obtained from both the literature and innovator drug companies for over one half (45 of 68) of these items. A summary of recommendations for use in cold operations of these 68 items was prepared. Recommendations ranged from conservative (in those cases where no information was available) to liberal (where drug companies were concerned with efficacy). Recommendations also included the substitution of some items on the list with drugs of similar action but not needing freeze protection.

Introduction

Winter warfare conducted in near-freezing and sub-freezing conditions presents problems generally not experienced in operations carried out at mild temperatures. Among these problems are the effects of low temperatures on medical equipment and supplies (3). A 1977 tri-service report (5) indicated that a pressing need exists to evaluate all medical items used in a climate categorized as #7 arctic (-30°C to -40°C). The effects of freeze/thaw cycles on pharmaceuticals are of great importance to medical support of cold weather operations. Thus, in order to evaluate these effects a comprehensive literature review was performed to assess published information and a survey of the innovator drug companies was conducted to obtain any additional unpublished data.

DRUGS OF OPERATIONAL IMPORTANCE

The 668 Authorized Medical Allowance List (AMAL)(4) for a mobile surgical hospital company is the largest, most sophisticated and complete list of materials and supplies available. This AMAL includes all drugs used by corpsmen in the field and at the battalion aid station levels as well as those used in a six operating room hospital. Furthermore, these drugs may be exposed to extreme cold during winter warfare operations. Therefore, the pharmaceuticals contained in the 668 AMAL were used as a basis for this study.

A thorough search of the drug literature produced little relevant information on the listed drugs. The only paper relevant to this study was that of Fure, et al (2) dealing with dextran solutions. Additionally, a review article published by Cutie (1), contained valuable general information on the state of different groups of drugs after freezing. Little attention, however, is given to individual drugs.

To obtain definitive information on individual drugs in the 668 AMAL, innovator drug companies were contacted for data on freezing and thawing of drugs which they had patented. Companies that innovate drugs are required to follow an established Food and Drug Administration (F.D.A.) testing protocol which does not include freezing and thawing. In many cases, however, freezing and thawing studies had been performed on specific drugs, although exposure time and temperatures did not conform to a set protocol. The results from this survey are listed in Tables I and II. These tables list in alphabetical order all the drugs identified on the 668 AMAL as needing freeze protection. Table I contains the name of the drug and its corresponding federal stock number. The symbols appearing before some of the stock numbers indicate whether the drug is or is not damaged by freezing and whether substitute drugs are available which can withstand freezing. Those drugs without symbols indicate definitive information was unavailable. Table II contains the name of the drug, information from innovator companies and recommendations for use in cold weather operations, as well as substitute drugs available where applicable. This list is consecutively numbered and can be directly cross-referenced with Table 1.

SUMMARY

A list of drugs identified as being damaged by freezing (68 of 153 items) was excerpted from the 668 Authorized Medical Allowance List (AMAL). Freeze/thaw stability data was obtained from both the literature and innovator drug companies for over one half (45 of 68) of these items. A summary of recommendations for use in cold operations of these 68 items was prepared. Recommendations ranged from conservative (in those cases where no information was available) to liberal (where drug companies were concerned about efficacy). Recommendations also included the substitution of some items on the list with drugs of similar action but not needing freeze protection.

REFERENCES

1. Cutie, M. R. Effect of cold and freezing temperatures on pharmaceutical dosage forms. Drug and Cosmetic Industry, 126(1): 40-43: 86, 1980.

2. Fure, O. T., Karlsen, J., Warnhus, K. A. and Waller, T. On the stability of dextran solutions. Pharmaceutica Acta Helvetiae, 50: 216-218, 1975.

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4. Naval Medical Material Support Command. 668 Authorized Medical Allowance List for Hospital Company, Medical Battalion Force Service Support Group, FMF. Phila., PA. 31p.

5. Office of Naval Research and U. S. Army Research Institute of Environmental Medicine - Joint Meeting. Problems of Medical Evacuation in Cold Weather, 1977, 59 p.

TABLE I

DRUGS AND RELATED ITEMS IDENTIFIED ON 668 AMAL AS NEEDING FREEZE PROTECTION

* Damaged by Freezing (Substitute Available)
† Damaged by Freezing (No Substitute Available)
§ Not Damaged by Freezing.

Drugs without symbol indicate definitive information was unavailable

1.	Acetaminophen Elixir, USP	*6505 - 00 - 148 - 7126
2.	Albumin, Normal Human Serum, USP	§6505 - 00 - 299 - 8179
3.	Aminophylline Injection, USP	†6505 - 00 - 105 - 9500
4.	Antidote, Nerve Agents	6505 - 00 - 134 - 2943
5.	Atropine Sulfate Injection, USP	6505 - 00 - 754 - 2547
6.	Calcium Gluceptate Injection, USP	§6505 - 00 - 559 - 5143
7.	Chlorpromazine Hydrochloride Injection, USP	†6505 - 00 - 597 - 5843
8.	Clindamycin Phosphate Injection, N.F.	§6505 - 00 - 139 - 1318
9.	Dexamethasone Sodium Phosphate Injection, USP	*6505 - 00 - 963 - 5355
10.	Detergent, Surgical Povidone-Iodine 7.5%, 4 oz. bottle	6505 - 00 - 491 - 7557
11.	Detergent, Surgical Povidone-Iodine 7.5%, 1 gallon	6505 - 00 - 994 - 7224
12.	Dextrose Injection, USP 5% I.V. Bag	§6505 - 00 - 083 - 6538
13.	Dextrose Injection, USP 10% 3 ml Ampul	§6505 - 00 - 116 - 4603
14.	Dextrose in Lactated Ringer's Solution 5%, 500 ml Bag	§6505 - 00 - 116 - 1060
15.	Dextrose in Lactated Ringer's Solution 5%, 1000 ml Bag	§6505 - 00 - 116 - 1064
16.	Dextrose 5% in 0.45% Sodium Chloride Solution	§6505 - 00 - 116 - 1025
17.	Digoxin Injection, USP	§6505 - 00 - 531 - 7761
18.	Diphenhydramine Hydrochloride Injection, USP, 10 ml Bottle	§6505 - 00 - 299 - 8611
19.	Diphenhydramine Hydrochloride Injection, USP, 1 ml Syringe	§6505 - 00 - 148 - 7177
20.	Ephedrine Sufate Injection, USP	6505 - 00 - 117 - 4904

TABLE I--continued

21.	Epinephrine Injection, USP	6505 - 00 - 133 - 4449
22.	Fentanyl Citrate Injection, USP	6505 - 01 - 010 - 4170
23.	Flurandrenolide Cream, USP	6505 - 00 - 890 - 1554
24.	Formaldehyde Solution, USP	*6505 - 00 - 139 - 1321
25.	Furosemide Injection, USP	§6505 - 00 - 435 - 0377
26.	Gentamicin Sulfate Injection, USP	§6505 - 00 - 181 - 7180
27.	Glycopyrrolate Injection, N.F.	6505 - 00 - 279 - 7691
28.	Guaifenesin Syrup, N.F.	§6505 - 00 - 064 - 8765
29.	Heparin Sodium Injection, USP 1000 units/ml, 10 ml bottle	§6505 - 00 - 153 - 9740
30.	Heparin Sodium Injection, USP 10,000 units/ml, 5 ml bottle	§6505 - 00 - 584 - 2914
31.	Hexachlorophene Detergent Lotion, USP	6505 - 00 - 149 - 0746
32.	Hydrocortisone Cream, USP	6505 - 00 - 926 - 2095
33.	Hydrocortisone Sodium Succinate for Injection, USP	§6505 - 00 - 753 - 9609
34.	Hydrogen Peroxide Solution, USP	§6505 - 00 - 153 - 8480
35.	Insulin Injection, USP	†6505 - 00 - 584 - 3470
36.	Isoproterenol Hydrochloride Injection, USP	§6505 - 00 - 890 - 1289
37.	Ketamine Hydrochloride Injection, N.F.	6505 - 00 - 432 - 7047
38.	Lidocaine Hydrochloride Injection, USP 20 ml Bottle without epinephrine	§6505 - 00 - 598 - 6117
39.	Lidocaine Hydrochloride Injection, USP 50 ml bottle without epinephrine	§6505 - 00 - 598 - 6116
40.	Lidocaine Hydrochloride Injection, USP 2% with epinephrine in syringe	§6505 - 00 - 576 - 8842
41.	Magnesia and Alumina Oral Suspension, USP	*6505 - 00 - 680 - 0133
42.	Magnesium Sulfate Injection, USP	6505 - 00 - 126 - 5100
43.	Mannitol Injection, USP	†6505 - 00 - 889 - 6653
44.	Meperidine Hydrochloride Injection, USP, 50 mg cartridge needle 1 ml	§6505 - 00 - 855 - 6979

TABLE I--continued

45.	Meperidine Hydrochloride Injection, USP 100 mg cartridge needle 1 ml	§6505 - 00 - 855 - 6984
46.	Methylprednisolone Sodium Succinate for Injection, USP	§6505 - 00 - 104 - 8069
47.	Milk of Magnesia, USP	*6505 - 00 - 148 - 7263
48.	Morphine Sulfate Injection, USP	6505 - 00 - 149 - 0112
49.	Naloxone Hydrochlorine Injection, USP	†6505 - 00 - 079 - 7867
50.	Neostigmine Methylsulfate Injection, USP	6505 - 00 - 958 - 6325
51.	Pancuronium Bromide Injection	6505 - 01 - 012 - 7559
52.	Pentobarbital Sodium Injection, USP	6505 - 00 - 133 - 5489
53.	Phentoin Sodium Injection	6505 - 00 - 139 - 4348
54.	Potassium Chloride Injection, USP	†6505 - 00 - 299 - 9505
55.	Prochlorperazine Edisylate Injection, USP	6505 - 00 - 656 - 1610
56.	Ringer's Injection Lactated, USP	§6505 - 00 - 083 - 6537
57.	Scopolamine Hydrobromide Injection, USP	§6505 - 00 - 926 - 8967
58.	Sodium Bicarbonate Injection, USP	†6505 - 01 - 053 - 2634
59.	Sodium Chloride Injection, USP 5 ml Ampul	§6505 - 00 - 559 - 8456
60.	Sodium Chloride Injection, USP I.V. Bag	§6505 - 00 - 083 - 6544
61.	Succinylcholine Chloride, Sterile, USP	§6505 - 00 - 133 - 4909
62.	Tetanus Toxoid, USP	†6505 - 00 - 680 - 2433
63.	Tetracaine Hydrochloride Injection, USP	6505 - 00 - 290 - 6034
64.	Thiopental Sodium for Injection, USP	6505 - 00 - 117 - 9204
65.	Thrombin, USP	6505 - 00 - 161 - 2950
66.	Tuberculin, USP	6505 - 00 - 105 - 0102
67.	Tubocurarine Chloride Injection, USP	§6505 - 00 - 619 - 7703
68.	Water for Injection, Sterile, USP	§6505 - 00 - 543 - 4048

TABLE II

1. Acetaminophen Elixir - Lederle Laboratories recommends that this product should not be subjected to freezing temperatures

   The Elixir contains 120 mg/5 ml. Usual dose is 325 to 650 mg every 4 hours. The 668 AMAL contains about 550 minimum doses. Since freezing can damage both the Elixir and container the substitute should be Acetaminophen Tablets N.F. 325 mg/tablet. 500-600 tablets should be included in the AMAL for cold weather operations.

2. Albumin, Normal Human Serum, USP - Hyland Pharamaceutical - Div. of Travenol Laboratories recommends that freezing will not harm the solution but might damage container and permit contamination of contents.

3. Aminophylline Injection - Searle Laboratories recommend this product not be frozen.

   In an emergency situation there is no substitute for Aminophylline Injection. Special precautions must be taken to prevent this drug from freezing.

   As a smooth muscle relaxant Aminophylline is most effective when given intravenously. Absorption from G.I. tract after oral or rectal administration is slow, incomplete, and variable.

   However, for cold weather operations, it is recommended that tablets (200 mg Aminophylline), and 250 mg suppositories be included in the AMAL for maintenance dose purposes.

4. Antidote, Nerve Agent - Assay of drug was not available from Rodana Research Corporation. Their studies have involved testing only the function of the COMBO-BEN container after freezing and thawing and have found it to be satisfactory.

5. Atropine Sulfate - Definitive information was not obtained for this drug.

6. Calcium Gluceptate - Lilly Inc. indicated that drug is not damaged by freezing but 5 ml Ampul will probably break.

   We recommend that disposable prefilled syringe be used instead of ampul for cold weather operations since it is less likely to break.

   Pre-filled syringe manufactured by Abbott Laboratories, 5 ml Abboject unit of use syringe with 22½ G, 1½ inch needle list no. 4907.

7. Chlorpromazine Hydrobromide Injection - Wyeth Laboratories Inc. indicated that the drug will be damaged by freezing.

   It is not recommended that tablets be substituted for the injection in cold weather operations.

   Special precautions should be taken to prevent freezing of this drug.

TABLE II--continued

8. Clindamycin Phosphate Injection - The Upjohn Company indicated that a solution of 6 mg/ml Clindamycin Phosphate in Dextrose 5% in water did not deteriorate even after being frozen for 79 days at -10°C. However, they do not have data of prolonged freezing and then use of undiluted Clindamycin Phosphate solutions.

   Depending on need, it is recommended that a quantity of this drug be diluted into Dextrose 5% I.V. solutions prior to cold weather operations.

9. Dexamethasone Sodium Phosphate - At this time no data has been obtained from the innovator company; however, Towne Paulsen Pharmaceuticals which markets this product recommends against using it if frozen.

   Therefore, it is our recommendation that until confirmation of potency after freezing is obtained, Dexamethasone USP tablets in various dosage forms should be included in the AMAL for cold weather operations. Dexamethasone USP has the same actions as Dexamethasone Sodium Phosphate, USP.

   Practitioners may also consider substitution of Hydrocortisone Sodium Succinate for Injection (#33) or Methylprednisolone Sodium Succinate for Injection (#46) in place of Dexamethasone Sodium Phosphate except for status asthmaticus.

10. & 11. Detergent, Surgical Povidone-Iodine 7½% - Information on this product was unavailable.

Prepared I.V. Solutions in Plastic Bags

12. Dextrose Injection 5%, USP
13. Dextrose Injection 10%, USP
14. Dextrose in Lactated Ringer's Solution 5%, 500 ml
15. Dextrose in Lactated Ringer's Solution 5%, 1,000 ml
16. Dextrsoe in 0.45% Sodium Chloride Solution
56. Ringer's Injection Lactated
60. Sodium Chloride Injection

The stability of Dextran solution submitted to rough storage and treatment was studied by Fure, et al, 1975.

The Dextrose they studied was 6% solution of Macrodex by Pharmacia which is similar to the Dextrose used as a base for the I.V. injections numbered 12 through 16. The solutions were shaken, frozen, and thawed according to a fixed schedule, and pH, buffer capacity, and molecular weight distribution were checked before and after treatment. A long-lasting shaking of partly frozen dextran solution had no influence on the analytical data. A freezing/thawing cycle repeated 50 times showed the same results. No significant change in pH, buffer capacity, or molecular weight distribution could be detected. They concluded that Dextran solutions can be stored for a long time and even be subjected to extreme temperature changes which cause the solution to freeze, without changing the Dextran molecular weight distribution.

The additional ingredients in numbers 14, 15, 16, 56, and 60 are all soluble after freezing. In Lactated Ringer's Solution sodium chloride, calcium chloride, potassium chloride and sodium latate are added.

It is our opinion that all the above I.V. solutions will present no operational problems in a cold weather environment from the standpoint of drug protency.

17. Digoxin, USP - Burrows-Wellcome Co. reported that on the basis of laboratory studies to evaluate the effects of freezing, Digoxin was subjected to three repeated freeze-thaw cycles consisting of 8 hours freezing and 16 hours thawing. The assay tests performed showed no significant change in drug potency after freezing and thawing. Also there was no apparent failure of the packaging components.

    It is our recommendation that Digoxin in 2 ml ampuls is safe for use after freezing and thawing.

18. Diphenhydramine Hydrochloride Injection, 10 ml Bottle
19. Diphenhydramine Hydrochloride Injection, 1 ml Syringe

    Parke-Davis & Co reports that Diphenhydramine Hydrochloride can be frozen and thawed without any adverse effects on the drug except in 1% of the cases the drug will non-reversibly precipitate.

    We recommend that for cold weather operations only the 1 ml syringe be used since each one can be carefully inspected for precipitate prior to use. The 10 ml multi-dose bottle should not be used since it is more difficult to see precipitate in the bottle. Also a larger amount of the drug would have to be discarded if precipitate was found in the bottle and the bottle is more subject to packaging failure.

    As an alternative, Diphenhydramine Hydrochloride Capsules should also be included in the AMAL for cold operations but are not recommended for emergency situations. 25 mg capsules and 50 mg capsules are available in bottles of 100 and 1,000 from Parke-Davis.

20. Ephedrine Sulfate Injection - Information was not available for this drug.

21. Epinephrine Injection - No definitive information was available on this drug.

22. Fentanyl Citrate Injection - Information on the drug is presently not available from Critikon.

23. Flurandrenolide Cream - Specific information as to potency after freezing and thawing of this drug was not available; however, the drug should normally be stored in the cold to protect it.

24. Formaldehyde Solution - Formaldehyde will freeze and possibly solidify depending on the temperature and in almost every case, break the glass container.

    We recommend for this product that the solution be transferred to thick walled plastic bottles and only partially filled for cold weather operations.

25. Furosemide Injection - Hoechst-Roussel Pharmaceuticals report that furosemide will freeze but may be used after being brought to room temperature with no significant loss of potency. If there is evidence of cracking, leaking, or crazing of the glass ampul, it should not be used. All intact ampuls when returned to room temperature should be vigorously shaken to redissolve any constituents that may have crystallized out of solution. These constituents are usually very rapidly dissolved and present no difficulty. When the solution is clear and free of undissolved matter, the injection is safe to use or store as if never frozen. Should any ampul be found that does not become clear and free of any visible particulate matter after vigorous shaking, it should not be used.

TABLE II--continued

26. Gentamicin Sulfate Injection - The Schering Corporation reports this products has been subjected to freeze/thaw cycles of 24, 48, 72, and 96 hours and that no significant loss of potency has been observed for any of these time periods.

    We feel that this product packaged in the 2 ml bottle is completely satisfactory for usage in a cold weather environment, however, we recommend the user should carefully inspect the bottle and septum seal prior to use.

27. Glycopyrrolate Injection - Information was not available.

28. Guiafenesin Syrup - Philips Roxane Laboratories, Inc. have indicated that Guiafenesin Syrup is not harmed by freezing.

    Glass bottle packaging may present a problem in a cold weather environment.

29. Heparin Sodium Injection, 1000 units/ml (10 ml bottle)
30. Heparin Sodium Injection, 10,000 units/ml (5 ml bottle)

    Organon Pharmaceuticals, The A. H. Robins Co., and Riker Laboratories, Inc., all have indicated their heparin products freeze but may be safely used when thawed if the bottles are not damaged. There is a possibility that the heparin may have to be shaken back into solution but freezing has no effect on the ingredients of this product.

    We recommend these products for use in cold weather operations.

31. Hexachlorophene Detergent Lotion - Information was unavailable for this product.

32. Hydrocortisone Cream - Information was not obtained for this product.

33. Hydrocortisone Sodium Succinate for Injection
46. Methylprednisolone Sodium Succinate for Injection

    The Upjohn Co. indicated their in-house studies have shown that reconstituting and freezing both products listed above does not adversely affect potency stability. However, solutions of both these products should be used within 48 hours after reconstitution. Solutions from the thawed products should also be used within 48 hours.

    They were not able at this time to provide us with data regarding the effects of freezing on levels of free steroid. They speculated that the stability of I.V. solutions prepared from both of the above thawed products theoretically could be affected by levels of free steroid, pH, and solution concentration.

    For cold weather operations, we recommend that both products be left in the lyophylized form and not reconstituted until needed. The packaging of the Hydrocortisone Sodium Succinate may be damaged by freezing since the liquid diluent is separated by a rubber stopper from the lyophylized powder. If on inspection prior to use it appears that the liquid may have leaked into the powder, do not use that container.

34. Hydrogen Peroxide Solution - The J. T. Baker Chemical Co. has indicated that H_2O_2 will not degrade significantly by repeated freezing and thawing but will quickly lose strength in excessive heat.

    A study done in our lab with H_2O_2 packaged in brown plastic containers has shown no loss of stability and the containers have maintained their integrity upon numerous freeze/thaw cycles.

    It is our recommendation that this product is safe for use in a cold weather operation.

35. Insulin Injection - Eli Lilly and Company reports that freezing the various insulin (ILETIN TM) products does not tend to affect the potency. REGULAR ILETIN will return to its normal state after freezing, if it is allowed to thaw out gradually, provided no other adverse conditions have been encountered. The modified ILETIN products may or may not be satisfactory for use after they have thawed. Freezing has a tendency to cause the fine particles of the precipitate in the modified ILETIN products to clump into particles of various sizes. If clumpling has occurred, uniform resuspension of the precipitate is impossible and uniform doses cannot be withdrawn from the vials. Use of such material may very well cause an erratic response.

    The modified ILETIN products; such as PROTAMINE ZINC AND ILETIN, NPH ILETIN, and LENTE ILETIN, are most apt to be affected by freezing. The effect of freezing may be alteration of the protein material in PROTAMINE, ZINC AND ILETIN and NPH ILETIN. It may be that the nature of the protein is not affected, but that the fine particles of the precipitate are caused to adhere and form clumps which cannot be uniformly dispersed throughout the liquid.

    LENTE ILETIN products are affected because of changes produced, or probably produced, in the characteristics of the precipitate. Changes during and after freezing might occur in the particle or crystal characteristics of some of the components of the LENTE ILETIN material.

    They also pointed out that exposure to abnormally high temperatures will have a very similar effect on the modified ILETIN products in that clumping of the fine particles of the precipitate will occur. They make it a general rule to advise that all ILETIN products which have been frozen should not be used.

    We also recommend this product <u>not</u> be used if frozen.

36. Isoproterenol Hydrochloride Injection - Breon Laboratories reported that in-house studies indicate freezing does not affect the potency stability of Isoproterenol Hydrochloride. The drug may be used after thawing as long as the solution is perfectly clear and shows no signs of precipitation or cloudiness. Ampuls should also be examined for physical damage.

    We feel that this drug is safe for use in cold weather operations and to help prevent ampul failure, should be used only in the 1 ml ampul size.

37. Ketamine Hydrochloride Injection - Information was unavailable for this product.

38. Lidocaine Hydrochloride Injection, 20 ml BT without Epinephrine
39. Lidocaine Hydrochloride Injection, 50 ml BT without Epinephrine
40. Lidocaine Hydrochloride Injection, 2% with Epinephrine in Syringe

    Astra Pharmaceuticals has determined through their in-house studies that all the above listed products are safe to use after freezing provided that the containers are completely intact and solutions remain clear upon thawing.

    We recommend these products safe for cold weather operations.

41. Magnesia and Alumina Oral Suspension - Philips Roxane Laboratories, Inc. reports thatMagnesia and Alumina Oral Suspension <u>is</u> damaged by freezing and should <u>not</u> be used.

    We recommend this Suspension <u>not</u> be used in any cold weather operation. As an alternative, Magnesia and Alumina Tablets with 200 mg of each ingredient should be substituted.

42. Magnesium Sulfate Injection - Information was not obtained for this drug.

43. Mannitol Injection - Merck Sharp and Dohme reported that their quality control department has not conducted studies to evaluate the effects of freezing and thawing on mannitol either within the vials as sold or otherwise.

    The data from our own container study indicate that the 50 ml ampul is extremely fragile and will undoubtedly fail if the solution is allowed to freeze.

    Special precautions should be taken to prevent freezing of this drug.

44. Meperidine Hydrochloride Injection, 50 mg Cart. Needle 1 ml
45. Meperidine Hydrochloride Injection, 100 mg Cart. Needle 1 ml

    Winthrop Laboratories has found that Meperidine Hydrochloride Injection can be used after thawing as long as the solution is perfectly clear and shows no signs of cloudiness.

    We recommend these products for cold weather operations.

46. See #33.

47. Milk of Magnesia - Both the Parke-Davis & Co. and Philips Roxane Laboratories, Inc. have indicated that Milk of Magnesia may be difficult to resuspend after freezing and both advise against its use. However, Concentrated Milk of Magnesia is not harmed by freezing and it is our recommendation that this product be substituted in place of dilute Milk of Magnesia for cold weather operations.

48. Morphine Sulfate Injection - Information was unavailable for this product.

49. Naloxone Hydrochloride Injection - Endo Laboratories Inc. conducted extensive quality control stability tests on this product and have determined that it is not safe to use after freezing and thawing.

    We recommend that this drug not be used if frozen. Since it is a very important drug and no substitute is available, special precautions must be taken to keep it from freezing.

50. Neostigmine Methylsulfate Injection - Information was not available on this drug.

51. Pancuronium Bromide Injection - Information was not available for this drug.

52. Pentobarbital Sodium Injection - Information on this drug is not presently available.

53. Phentoin Sodium Injection - Information was not available for this drug.

54. Potassium Chloride Injection - Lederle Laboratories has determined that Potassium Chloride liquids are not safe to use after freezing and thawing. KCL may crystallize out of solution upon freezing and may not re-dissolve upon thawing.

    We recommend that Potassium Chloride Injection not be used if frozen. This is a very important drug with no substitutes, hence, special precautions must be taken to keep it from freezing.

55. Prochlorperazine Edisylate Injection - No information was available for this drug.

56. See #12.

57. Scopolamine Hydrobromide Injection - Burroughs Wellcome Co. subjected this drug to three repeated freeze/thaw cycles consisting of 8 hours freezing and 16 hours thawing. They reported that no physical changes occurred after the third thawing, and the assay showed no significant decline in potency stability. There was also no apparent failure of the packaging.
We recommend this drug can be used in a cold weather operation in no larger than 1 ml ampuls.

58. Sodium Bicarbonate Injection - Freezing will destroy the 50 ml ampul in every case, however, freezing has no effect on the drug itself.
We recommend this drug be kept from freezing since there is no substitute.

59. Sodium Chloride Injection, 5 ml Ampul - Freezing has no effect on drug but container must be carefully inspected prior to use after thawing.

60. Sodium Chloride Injection (I.V.) - See #12 Dextrose Injection for I.V. solutions.

61. Succinylcholine Chloride, Sterile - Burroughs Wellcome Co. reported that Succinylcholine Chloride Injection after 3 freeze/thaw cycles showed no significant decrease in potency stability. Also no apparent failure in the packaging was recorded.
We recommend that this drug is safe for use in a cold weather operation.

62. Tetanus Toxoid - Lederle Laboratories report that Tentanus Toxoid <u>should not</u> be administered in any form and under any conditions if frozen or even suspected of having been frozen. Their research indicates that freezing may break down the drug into toxic by-products.
We recommend that this product be protected at all times from freezing since there are no substitutes which can be frozen.

63. Tetracaine Hydrochloride Injection - Information was not availabe for this drug.

64. Thiopental Sodium for Injection - Information was not available for this drug.

65. Thrombin - Information was not available for this drug.

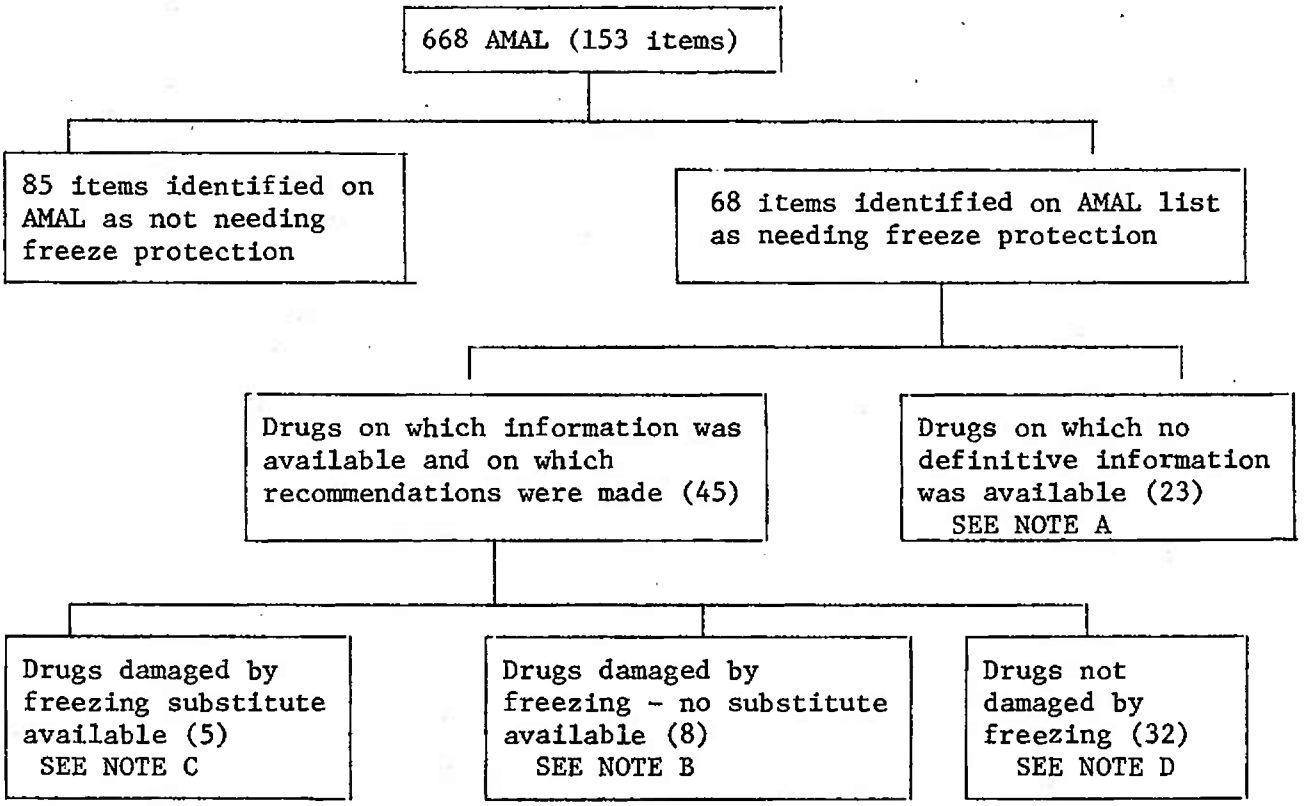
66. Tuberculin - Information was not available for this drug.

67. Tubocurarine Chloride Injection - Eli Lilly and Co. reported that they have no data on frozen solutions of Tubocurarine Chloride Injection. Their product contains, in addition to the active ingredient, Chlorobutanol Sodium Chloride, Sodium Bisulfite, and Water for injection. If upon thawing this solution retained its normal clear colorless appearance, it is highly unlikely the activity would be affected. This, however, is merely their opinion.
We recommend that this drug <u>not</u> be used if frozen. Substitute Calcium Gluceptate (#6 on list) if freezing does occur.

68. Water for Injection - Freezing of this product only presents a packaging problem. We recommend that before use, each bottle be carefully inspected.

FLOWCHART FOR SUMMARY OF RECOMMENDATIONS

Given: That all drugs and related items are frozen as a result of operations carried out in a cold environment



NOTE A: For drugs on which no definitive information was available, we recommend that these items be kept from freezing in the manner described in NOTE B. This applied especially to the injectable products. We further recommend that these drugs and those which do not appear on this list and added to new or updated AMALS be scrutinized through in vitro testing or innovator company data.

NOTE B: A total of 8 drugs on this list have definitively been identified as damaged by freezing with no available substitute (those marked † in Table 1). We recommended these drugs must be kept from freezing under all circumstances. In order to carry out this task, a special heated chest should be employed similar to the one used by the Norwegian Military (Personal communication, Per Olay Roksvaag, Norwegian Joint Medical Service, Norway). At this time we do not have specifications on this chest, but it is apparently electrically heated and well insulated. Additionally, the total cubic foot volume of the 8 labile drugs carried in the 668 AMAL is about 7.5 cu ft. This volume could easily fit into one or two small chests specifically designed to accommodate the various boxes of drugs.

NOTE C: Substitutes for 4 of these drugs need to be included in the AMAL prior to mount out. One substitute is already included in the AMAL. All substitutes can be frozen.

NOTE D: Drug manufacturers indicate on bottles, ampuls, vials, etc. those products that need freeze protection. This is a usual precautionary measure taken by the companies resulting from the fact containers often fail when their contents are frozen. However, 32 of the 68 items on the 668 AMAL can be frozen and used, provided containers are intact upon thawing.

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A list of drugs identified as being damaged by freezing (68 of 153 items) was excerpted from the 668 Authorized Medical Allowance List (AMAL). Freeze/thaw stability data was obtained from both the literature and innovator drug companies for over one half (45 of 68) of these items. A summary of recommendations for use in cold operations of these 68 items was prepared. Recommendations ranged from conservative (in those cases where no information was available) to liberal (where drug companies were concerned with efficacy). Recom-

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mendations also included the substitution of some items on the list with drugs of similar action but not needing freeze protection.